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Oxford BioMedica

Risk-sharing in cystic fibrosis gene-therapy

OXB is a specialist, advanced-therapy, lentivirus vector biopharma company. It offers vector manufacturing and development services and has a proprietary drug pipeline. In addition to LentiVector® service contracts, OXB receives royalties on commercial therapies developed by its partners using the LentiVector platform. A partnership deal structure was established with Novartis for Kymriah™ in 2017, followed by a collaboration with Bioverativ in February 2018 and by out-licensing its Parkinson's disease gene-therapy to Axovant in June 2018. In August, OXB announced a second 2018 collaboration agreement, for cystic fibrosis gene-therapy.

- **Strategy**: OXB has four strategic objectives: delivery of process development (PD) services that embed its technology in partners' commercial products; commercial manufacture of lentiviral vector; out-licensing of proprietary candidates; and investment in R&D and the LentiVector platform.
- **New partnership:** the collaboration to develop a cystic fibrosis (CF) gene-therapy involves technology transfer by OXB of a lentivirus-based gene-therapy from the CF Gene Therapy Consortium/Imperial Innovations to OXB's platform. Separately, Boehringer Ingelheim has signed an option to license the therapy.
- **Promise in CF:** As a severe genetic disorder affecting over 70,000 people and with few licensed treatments, CF represents a huge unmet need for which an effective gene-therapy would represent a paradigm shift. This partnered, discovery-stage therapy has potential to be first-in-class, if successful.
- **Risks:** OXB's mid-term sales model and its ability to pay off debt are dependent on successful progress of partners' clinical trials and commercialisation of LentiVector-enabled products, for receipt of bioprocessing milestones and royalty payments. All gene-therapy candidates are subject to significant clinical risk.
- **Investment summary:** OXB is at a very interesting juncture. Heavy investment in state-of-the-art GMP manufacturing facilities for production of gene-therapy vector has resulted in supply agreements with Novartis, Bioverativ, AXON, and now in CF, on top of existing partnerships – positioning the group on the road to significant bioprocessing service income, milestones, and royalties.

Financial summary and valuation

Year-end Dec (£m)	2015	2016	2017	2018E	2019E	2020E
Sales	15.91	27.78	31.49	43.80	58.20	79.30
EBITDA	-11.73	-6.78	-2.63	15.68	15.83	25.51
Underlying EBIT	-13.35	-10.45	-7.00	11.25	10.98	20.20
Reported EBIT	-14.08	-11.32	-5.67	10.19	9.82	18.94
Underlying PTP	-16.25	-15.34	-15.88	6.87	6.91	16.17
Statutory PTP	-16.98	-20.31	-11.76	5.81	5.75	14.91
Underlying EPS (p)	-23.91	-21.00	-21.19	15.90	15.61	31.53
Statutory EPS (p)	-25.33	-29.95	-14.56	14.25	13.83	29.61
Net (debt)/cash	-17.90	-19.05	-22.54	-2.26	-4.37	5.76
Shares issued (m)	0.14	17.50	0.39	19.40	0.10	0.10
P/E (x)	-	-	-	-	-	27.8
EV/sales (x)	-	-	-	-	-	22.0

Source: Hardman & Co Life Sciences Research

Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data

EPIC/TKR	**OXB**
Price (p)	876
12m High (p)	1064
12m Low (p)	388
Shares (m)	65.7
Mkt Cap (£m)	576
EV (£m)	561
Free Float	63%
Market	LSE

**As defined by AIM Rule 26*

Description

Oxford BioMedica (OXB) is a UK-based biopharmaceutical company specialising in cell and gene therapies developed using lentiviral vectors – gene-delivery vehicles based on virus particles. In addition to vector development and manufacture, OXB has a pipeline of therapeutic candidates and undertakes innovative pre-clinical R&D in gene-medicine.

Company information

CEO	John Dawson
CFO	Stuart Paynter
Chairman	Lorenzo Tallarigo
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	www.oxfordBioMedica.co.uk

Key shareholders

Directors	0.3%
Vulpes	17.7%
M&G	17.7%
Canaccord Genuity	5.1%
Aviva	3.9%
Hargreaves Lansdown	3.7%
Shah	3.1%

Diary

Sep-18	Interims

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Collaboration and option agreement

Summary: OXB's third deal in 2018

Process development (PD) partnership in CF

OXB has entered into a PD partnership with the UK Cystic Fibrosis (CF) Gene Therapy Consortium (GTC) and Imperial Innovations, the technology transfer office of Imperial College London, to develop a gene-therapy for CF. OXB will transfer the technology discovered by the partners of the CFGTC to the LentiVector platform, thus making it suitable for potential clinical and commercial-scale bioprocessing. Key points are outlined below.

- **OXB licence:** We assume that OXB will have been granted rights to the CFGTC's intellectual property (IP) covering its viral vector CF gene-therapy candidate for a modest payment and/or royalty agreement.
- **OXB PD:** Transfer of CFGTC vector to the LentiVector platform; manufacture scale-up; bioprocessing for pre-clinical studies.
- **Clinical supply:** There is potential for a clinical supply contract in the future.

Option agreement with Boehringer Ingelheim

Separately, OXB has signed an option and license agreement with Boehringer Ingelheim (BI) for the exclusive global rights to OXB's lentiviral vector technology for the manufacture, registration, and commercialisation of the CF gene-therapy.

- The financial terms of the agreement with BI have not been disclosed. However, we have assumed in our model that a small payment was made to OXB by BI on signing the option agreement. We have not included additional milestone or incentive payments from BI in our forecasts at this early stage. However, it is likely that any payment from BI, should it opt to license, will be very significant.

OXB deals, 2017-18

Term	Novartis deal 2 extension*	Bioverativ	Axovant	UK CFGTC, Imperial Innovations /BI
Type	Manufacturing	Collaboration/licensing	Licensing	Collaboration/option
Year	2017	2018	2018	2018
Therapy area/type	Oncology, CAR-T cell-therapy	Haemophilia, *in vivo* gene-therapy	Parkinson's disease, *in vivo* gene-therapy	CF, *in vivo* gene-therapy
Duration	3-5 years	Unknown	Unknown	n.a.
Up-front on signing	$10m	$5m	$30m (incl. $5m designated for manufacturing)	Not disclosed
MS, incentives, service payments	$90m min.	$100m max (reg. & sales MS)	$812.5m max. (dev., reg. & sales MS)	Not disclosed
PD	Yes	Yes	**Yes – separately funded by Axovant**	Yes
Clinical supply	Yes	**Potential**	**Potential**	**Potential**
Commercial supply	Yes	No	**Potential**	**Potential**
Royalty	Yes	Yes	Tiered: 7%-10%	Not disclosed

MS: milestone payments; reg: regulatory; dev: clinical development

**For original Novartis deal terms, refer to our note 'Gene-therapy for Parkinson's: clinical progression' published 14 June 2018*

Source: Company announcements; Hardman & Co Life Sciences Research

CFGTC logo

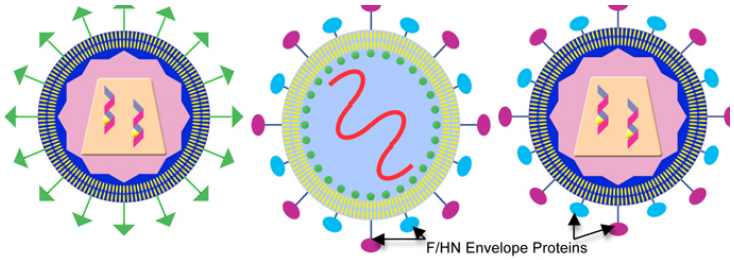
Source: cfgenetherapy.org.uk

Building on UK CFGTC technology

The UK CFGTC is a collaboration established in 2001 by Imperial College London and the Universities of Oxford and Edinburgh to investigate the feasibility of a gene therapy for clinical treatment of CF. CFGTC's first approach was to deliver the therapeutic gene to the cells of the lungs using a liposome vector as an aerosol. While this approach did show safety and efficacy in Phase I and II trials, the candidate did not appear to be more effective than the standard of care, most likely because the amount of therapeutic DNA successfully entering cells was too low.

The consortium's subsequent approach has been to focus on developing a viral vector, which should be more efficient in transforming target cells. Working with the Japanese Biotech company, DNAVEC, a candidate gene-therapy has been developed based on a lentivirus modified with envelope proteins from the Sendai virus (not a lentivirus) – increasing the ability of the vector to enter epithelial cells. Thus far, gene transfer using this approach in models has been log orders higher than the liposome-based therapy. It is this technology that will be developed as part of the new partnership with OXB and BI.

Gene-therapy lentivirus viral vector



Lentivirus	Sendai Virus	Sendai-Pseudotyped SIV
Long-lived expression	Short-lived activity	Long-lived expression
No airway tropism	High tropism for airways	High tropism for airways

SIV: simian immunodeficiency virus, a type of lentivirus
Source: UK Cystic Fibrosis Gene Therapy Consortium

Funding for viral vector development to date has come from the Medical Research Council and the Cystic Fibrosis Trust, and also from the Health Innovation Challenge Fund run by the Wellcome Trust and the Department of Health and Social Care. Going forward, BI and OXB will collaborate with the CFGTC to support clinical development, with, we assume, much of the financial support coming from BI.

Boehringer Ingelheim – option to license

In a separate agreement, OXB has signed an agreement with the private German pharmaceutical company BI, which gives the latter the option to license the therapy for manufacture, regulatory submission, and commercialisation. A small payment is likely to have been made on signing to secure the agreement, and it is also likely that this will be of a magnitude that offsets the cost of PD and bioprocessing for the toxicology studies. The option period, during which evaluation of the technology through clinical development will take place, is unknown.

The agreement acts as excellent validation of the potential of gene-therapy as a new treatment paradigm in CF, a huge unmet medical need globally, and for which there is no cure. The potential total deal value, including milestones and other payments on exercising the option to license, is likely to be significant.

A typical nebuliser device

Source: cfgenetherapy.org.uk

Not only is this BI's first gene-therapy programme, but CF treatment is also a large market, currently estimated at around $3bn. Approval of a gene-therapy would multiply the market almost immediately.

Administration and dosing

BI has a big respiratory focus (currently asthma, COPD, pulmonary fibrosis, and lung cancer) and, therefore, has the operational expertise needed for global commercialisation in this therapeutic area. A CF gene-therapy would need to be delivered as an aerosol via a nebuliser device, giving rise to a host of considerations in administration of the correct dose (vector genomes/kg). Delivery of a therapeutic dose of the gene encoding cystic fibrosis transmembrane conductance regulator (CFTR) requires a large volume of efficient vector, and dosing of viral vectors in gene-therapy is highly sensitive, owing to toxicity concerns.

OXB PD

Licensing partnership

This is the third deal for OXB in 2018. Like the Bioverativ deal, it requires OXB to perform the process and analytical development of the vector, transferring its partners' technology to the LentiVector platform to form new IP that will incur a royalty from BI should the therapy be successfully commercialised. Also as with the Bioverativ deal, there is the potential for OXB to be signed in as the bioprocessing partner to supply the vector for clinical trials, which would incur bioprocessing service fees. If the CF therapy is successful in the clinic, BI will take over manufacture for commercialisation and the regulatory submission process. Such deals are risk-sharing partnerships, whereby the development, clinical, and commercialisation risk is shared among the partners.

Advantages for OXB

- **Low PD risk:** low costs incurred; an existing technology.
- **Out-license LentiVector platform in CF:** a narrow indication, maximising licensing opportunities with additional partners.
- **Validation:** OXB's third 'big pharma' partner.
- **Opportunity:** CF treatment requires a high volume of vector, so this is a good opportunity to test the scale-up of OXB's bioprocessing technology. Furthermore, for the first time, OXB may trial its proprietary TRiP system.

OXB gene-based medicine licensing partnerships

Programme	Partner	Indications	Type	Stage
Kymriah	Novartis	Oncology: r/r ALL	CAR-T	Approved in US
Kymriah	Novartis	Oncology: r/r DLBCL	CAR-T	Approved in US
OTL-101	Orchard Therapeutics	Primary immune deficiency	*Ex vivo*	Phase III
CMB305	Immune Design	Sarcoma	*In vivo*	Phase II
LV305	Immune Design	Oncology	*In vivo*	Phase II
ND	Novartis	Oncology	CAR-T	Phase I/II
OTL-201	Orchard Therapeutics	Sanfilippo syndrome	*Ex vivo*	Pre-clinical
Other	Orchard Therapeutics	ND	ND	Pre-clinical
Other	Orchard Therapeutics	ND	ND	Pre-clinical
Factor VIII	Bioverativ (Sanofi)	Haemophilia A	*In vivo*	Pre-clinical
Factor IX	Bioverativ (Sanofi)	Haemophilia B	*In vivo*	Pre-clinical
CF	UK CFGTC	CF	*In vivo*	Pre-clinical

ND: not disclosed

Source: Hardman & Co Life Sciences Research

Investment summary

Gene-therapy deals

This new deal with the UK CFGTC and the separate option agreement with BI provides further validation of the LentiVector platform. The deal size has not been disclosed, but it has the potential to be very lucrative, should it be successful. It should be noted that there is significant clinical and commercialisation risk, notably:

- This gene-therapy will target only the lungs, which, although are the most at risk in CF, are not the only organs that suffer from inadequate CFTR protein. This will not be a 'curative' therapy, unlike the potential haemophilia and Parkinson's gene-therapies.
- The reimbursement landscape is unknown for gene-therapies in Europe and the US; NICE has rejected CF medicines on the basis of cost-effectiveness in the past.

Gene-therapy deals have been extremely large, depending on the developmental stage of the therapy, as detailed in our recent reports. Latest deals include:

- **Regeneron Pharmaceuticals/BlueBird Bio:** On 6 August 2018, these companies signed a collaboration, which includes an option to license, for development of CAR-T cell therapies – Regeneron's initial investment (for pre-clinical development) in Bluebird is $100m.
- **Akouos:** On 7 August 2018, the private biotech company, Akouos, raised $50m in its Series A financing for pre-clinical development of its AAV-based gene therapies for hearing loss.
- **Novartis/AveXis:** In April 2018, Novartis bought the US biotech company, AveXis, for $8.7bn, acquiring a Phase III gene-therapy for spinal muscular atrophy, in addition to expertise and other capabilities in gene-therapy.

Changes to forecasts

While a CF gene-therapy has the potential to be extremely lucrative, it is at an early stage, and the financial terms of the deal have not been disclosed. The cost of PD during the first stage of the partnership will be absorbed in our existing R&D cost forecasts for 2018 and 2019, in which we have already allowed for additional PD work. We have included a small payment in 'other income' in the 2018 financial year (estimated at €2m) from BI. At this point, we have not updated our forecasts to include predicted potential milestone or royalty payments – this will be reassessed on announcement of further developments.

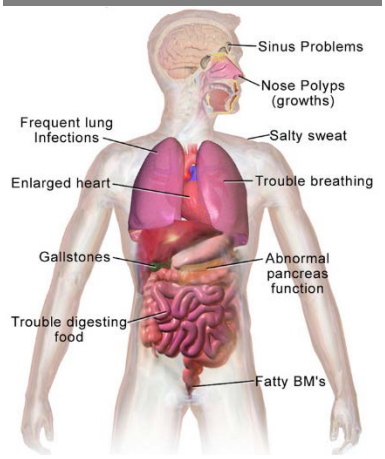
News flow

Value inflection points will include:

- an approval decision in Europe by the EMA on Novartis's Kymriah in B-ALL and DLCBCL;
- data from Orchard Therapeutics Phase III clinical trial; and
- OXB's interim results in September.

Gene-therapy for CF

Cystic fibrosis health problems



Source: Blausen gallery, 2014

CF

CF is a genetic disorder that affects approximately 1 in 3,000 Caucasian births, or 10,000 individuals in the UK and 70,000 worldwide. It is caused by a variety of mutations in both copies of the *CFTR* gene, which codes for the cystic fibrosis transmembrane conductance regulator (CTFR) ion channel protein of epithelial cell membranes. CFTR is involved in the maintenance of fluid and electrolyte balance in epithelial tissues in the body – an imbalance causes thick, sticky mucus and viscous secretions to accumulate in organs. CF most severely affects the lungs, where production of excessive quantities of thick sputum leads to difficulties in breathing and frequent lung infections. It also impacts the function of the pancreas, liver, kidneys, and intestine.

As an autosomal recessive disorder, both *CFTR* alleles must have at least one of 242 known CF-causing mutations for the disease to develop. Most of these mutations are very rare, with the majority of CF patients (up to 92%) harbouring the F508del mutation. Carriers (one mutated allele) tend to have sufficient functional protein.

Management of symptoms

There are a multitude of treatment options that can delay progression of the disease. However, because there is not yet a cure for the underlying genetic basis of the disease, the life expectancy of a CF patient is still around 40 years of age. Management of symptoms includes treating lung damage caused by thick mucus and infection, prevention of infection of the airways (for example, opportunistic *Pseudomonas aeruginosa* infections), and nutritional advice at specialist multidisciplinary centres. The total annual treatment for a single CF patient has been estimated to range from €19,581 to €68,696[1] depending on the country, and is £377,633[2] in the UK, thus the economic burden for payers is very large.

Marketed drugs

Vertex Pharmaceuticals

The landscape for new drugs to treat CF is dominated by Vertex Pharmaceuticals, which has three CF-specific marketed drugs. Kalydeco (chemical name ivacaftor) targets CFTR, and its usage has been expanded in patients with different gating mutations. Vertex's two combination treatments, Symdeko and Orkambi, include ivacaftor and are primarily indicated for patients with the F508del mutation. All are approved in the US and Europe. Sales of Orkambi comfortably exceeded $1bn in 2017; it is, however, in the midst of a reimbursement debate between NHS England and Vertex. At a cost of £100,000 p.a. per patient, Orkambi was rejected by NICE in 2016 on the basis of cost-effectiveness, in part because its efficacy is less than expected, given that it treats the mechanism of the disease (lumacaftor increases the amount of CFTR protein, and ivacaftor increases the activity of defective CFTR protein) rather than the symptoms of CF alone. It is, therefore, only available on the NHS on compassionate grounds.

Symdeko had sales of $34m in its first seven weeks on the market in 1Q'18.

[1] Kopciuch D et al. 2017 Public Health 148
[2] NICE Appraisal 2016 https://www.nice.org.uk/guidance/ta398/documents/committee-papers

Sales

The market for drugs used in the treatment of CF is very complex given that patients tend to use a wide range of drugs and health supplements. The following drugs have all been launched commercially, with CF as their specific indication; these specialist drugs alone create a worldwide market with annual sales over $3.0bn in 2017.

- **Pulmozyme** was launched by Roche in 1994 and is still selling at around $0.7bn p.a. by Genentech (Roche), with cumulative sales to date of $8.6bn. It is a recombinant engineered enzyme designed to break down the viscous sputum that is common in CF patients. To reach the required site of action, it is administered via a nebuliser. There are not yet biosimilar versions available.
- **TOBI** was launched by Novartis in 2006 and, until it was eroded by generic competition around 2013, sales were $300m p.a., with cumulative sales of $2.8bn to date. It is a specialist antibiotic against *Pseudomonas aeruginosa.*

CF drugs sales ($m)

Drugs	Manufact.	2010	2011	2012	2013	2014	2015	2016	2017	2018E
Orkambi	Vertex	0	0	0	0	0	351	980	1,320	1,200
Kalydeco	Vertex	0	0	172	371	464	632	703	845	1,050
Pulmozyme	Roche	492	55	572	617	652	678	695	742	765
Symdeko	Vertex	0	0	0	0	0	0	0	0	700
TOBI	Novartis	279	296	317	387	281	223	205	190	180
Total		**771**	**351**	**1,061**	**1,375**	**1,397**	**1,884**	**2,593**	**3,097**	**3,895**

Source: Hardman & Co Life Sciences Research

Developmental treatments

Gene-therapies

To our knowledge, there are not any gene-therapies for CF currently in clinical trials. Therefore, based on rapid progression to first-in-man trials, a gene-therapy developed by OXB and its collaborators has the potential to be first-in-class.

Editas Medicine, a US biotech company listed on Nasdaq (ticker: EDIT), is in a three-year partnership with the Cystic Fibrosis Foundation worth up to $5m to develop a CRISPR/Cas9-based gene editing medicine for CF. It is in the pre-clinical stage.

Galápagos Pharmaceuticals

In April 2018, Galápagos announced the initiation of its first clinical trial of a triple combination therapy targeting CFTR. This programme has been partnered with AbbVie since 2013.

Financial summary

- We have made no changes to our forecasts associated with the CF deal, except for an estimated €2m/£1.75m upfront payment to OXB in the second half of 2018 and minor increases in infrastructure costs in 2018 and 2019.
- We have updated the estimated royalty income from Kymriah sales in the US in 2018 and 2019 following the release of actual US numbers for 1H'18.

Financial summary

Year-end Dec (£m)	2015	2016	2017	2018E	2019E	2020E
GBP:EUR	1.38	1.18	1.14	1.14	1.14	1.14
GBP:USD	1.53	1.35	1.29	1.29	1.29	1.29
Profit & Loss						
Gross revenues	**18.77**	**30.78**	**39.36**	**74.80**	**79.10**	**105.80**
Bioprocessing + PD	**14.44**	**23.60**	**28.46**	**40.74**	**58.25**	**78.31**
Additional income	3.54	3.80	3.03	3.03	0.00	1.00
COGS	-5.84	-11.84	-18.44	-20.15	-31.43	-40.44
Gross profit	10.07	15.94	13.05	23.65	26.77	38.86
Gross margin	0.63	0.57	0.41	0.54	0.46	0.49
SG&A	-6.01	-5.09	-6.31	-15.33	-10.48	-9.52
R&D	-20.27	-24.30	-21.61	-28.03	-26.19	-35.69
EBITDA	-11.73	-6.78	-2.63	15.68	15.83	25.51
Other income	2.86	3.00	7.87	30.96	20.88	26.55
Underlying EBIT	-13.35	-10.45	-7.00	11.25	10.98	20.20
EBIT margin	0.84	0.38	-0.22	0.26	0.19	0.25
Net interest	-2.90	-4.89	-8.88	-4.38	-4.07	-4.03
Pre-tax profit	-16.25	-15.34	-15.88	6.87	6.91	16.17
Tax payable/credit	3.96	3.67	2.74	3.56	3.35	4.56
Underlying net income	-12.29	-11.67	-13.12	10.46	10.26	20.73
Weighted av. shares (m)	51.40	55.56	61.91	65.75	65.75	65.75
Underlying EPS (p)	**-23.91**	**-21.00**	**-21.19**	**15.90**	**15.61**	**31.53**
Fully diluted EPS (p)	-22.96	-20.12	-19.57	14.73	14.44	29.13
Balance sheet						
Share capital	25.74	30.88	31.08	32.88	32.88	32.88
Reserves	-14.85	-18.26	-24.38	2.59	11.79	31.36
Provisions	4.42	3.94	14.20	12.11	6.05	0.30
Debt	27.26	34.39	36.86	36.86	36.86	36.86
less: Cash	9.36	15.34	14.33	34.60	32.50	42.63
Invested capital	**33.21**	**34.95**	**40.48**	**46.88**	**52.13**	**55.82**
Net cash/debt	-17.90	-19.05	-22.54	-2.26	-4.37	5.76
Cashflow						
Operating profit	-13.35	-10.45	-7.00	11.25	10.98	20.20
Change in working capital	-4.09	1.25	-9.13	-2.58	-3.42	-3.99
Tax & interest	1.79	0.87	-7.25	-1.62	-0.49	-0.68
Operational cashflow	**-14.87**	**-5.93**	**-0.22**	**12.36**	**8.24**	**16.78**
Capital expenditure	-16.72	-6.46	-1.97	-9.87	-9.96	-6.06
Free cashflow	**-29.80**	**-11.52**	**-9.44**	**0.88**	**-2.21**	**10.03**
Acquisitions	0.00	0.00	0.00	0.00	0.00	0.00
Share issues	0.14	17.50	0.39	19.40	0.10	0.10
Change in net debt	**-31.10**	**-1.15**	**-3.48**	**20.28**	**-2.11**	**10.13**
Hardman FCF/sh. (p)	-25.45	-9.11	-12.06	16.34	11.79	24.48

Source: Hardman & Co Life Sciences Research

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(Disclaimer Version 8 – Effective from August 2018)

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The full detail is on page 26 of the full directive, which can be accessed here: http://ec.europa.eu/finance/docs/level-2-measures/mifid-delegated-regulation-2016-2031.pdf

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